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Drug-excipient interactions resulting from powder mixing. V. Role of sodium lauryl sulfate

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Summary

The effect of sodium lauryl sulfate on the drug-excipient interactions resulting from prolonged powder mixing with magnesium stearate was evaluated. Two formulations, identical in their composition, with and without 0.1% sodium lauryl sulfate were compared under identical mixing conditions to study the drug-excipient interaction on prolonged mixing and its effect on in vitro dissolution from hand-filled, uncompacted capsules. The results of this study reveal that the addition of sodium lauryl sulfate in the solid state to magnesium stearate in 1 : 5 ratio can offset the deleterious effects, such as the decrease in dissolution rate, associated with prolonged mixing of magnesium stearate. The results suggest that there is a strong physical interaction between the magnesium stearate flakes and sodium lauryl sulfate during the solid-state powder mixing process. The interaction between magnesium stearate and sodium lauryl sulfate frees the magnesium stearate flakes from the drug-excipient agglomerates. As a result, the capsule disintegration time and the drug dissolution rate are not adversely affected.

Introduction

Recent studies from our laboratories examined the interactions between the drug and the excipients which resulted from powder mixing. Two drugs, ketorolac tromethamine (Chowhan and Chi, 1985a,b) and prednisone (Chowhan and Chi, 1986a) were thoroughly mixed with a filler and a disintegrant with and without a lubricant. The powder mixtures were sampled at different mixing time intervals, examined under a scanning electron microscope and hand-filled into capsules for determining the effect of drug-excipient interactions on in vitro dissolution. The results of these investigations suggested:

(1) Prolonged mixing of a drug and excipients with magnesium stearate does not always reduce the rate of in vitro drug dissolution.

(2) Specific drug-excipient interactions occurred in powder mixtures containing ketorolac tromethamine, corn starch, lactose and magnesium stearate. Thorough mixing of these powders resulted in starch grain agglomeration, flaking and lamination of magnesium stearate and subsequent adhesion of these flakes to the agglomerated starch grains and drug particles. As a consequence, the drug dissolution rate decreased.

(3) Powder mixing of ketorolac tromethamine,

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pregelatinized starch and magnesium stearate with and without lactose did not show drug-excipient interactions and consequently, the in vitro dissolution from hand-filled capsules was unaffected. Similarly, thorough powder mixing of prednisone, pregelatinized starch and magnesium stearate did not exhibit drug-excipient interactions and the in vitro drug dissolution from hand-filled capsules was unaffected.

(4) Two distinctly different phenomena were observed when either ketorolac tromethamine, crospovidone and lactose or prednisone, dibasic calcium phosphate, dihydrate, potato starch or sodium starch glycolate with and without magnesium stearate were mixed:

(a) Thorough mixing without magnesium stearate resulted in drug-excipient interactions which caused lower drug recovery during dissolution testing.

(b) Prolonged mixing with magnesium stearate decreased the rate of drug dissolution due to interactions between magnesium stearate, drug and excipients.

(5) The use of sodium stearyl fumarate (Chowhan and Chi, 1986b) instead of magnesium stearate as a lubricant in the drug-excipient powder mixture prevented these interactions and their deleterious effect on drug dissolution. Thus, the crystal morphology of the lubricant also plays an important role in these interactions.

A mechanism for the role of lubricant materials as a function of mixing time was explored by Shah and Mlodozeniec (1977). The authors suggested that adsorption and delamination of the magnesium stearate particles is the mechanism that changes the statistics of the distribution of the stearate.

An earlier study by Levy and Gumtow (1963) compared the effect of two lubricants on the dissolution of salicylic acid from model compressed tablets. The results showed that water-soluble, surface-active lubricant (sodium lauryl sulfate) enhanced the drug dissolution rate whereas a hydrophobic lubricant (magnesium stearate) gave rise to retardation. The authors explained this phenomenon largely on the basis of the better penetration of solvent into the tablets and granules with the hydrophilic lubricant which exhibits surface-tension lowering capability and hence results in greater availability of drug surface. Another study by Murthy and Samyn (1977) investigated the influence of shearing on the in vitro dissolution property of several experimental capsule formulations containing either a hydrophobic (magnesium stearate) or a hydrophilic (magnesium lauryl sulfate) lubricant. The capsule formulations employed either a relatively water-insoluble or a water-soluble drug. The results of this study showed that there is a pronounced inhibitory effect on drug dissolution due to shearing in powder mixtures containing magnesium stearate. In systems with magnesium lauryl sulfate, the shear effect was less pronounced with water-insoluble drug or absent with water-soluble drug. However, the authors made no attempt to explain the mechanism of action of hydrophilic lubricant during shear mixing.

The drug and excipients which were previously shown to interact in the solid state during prolonged mixing resulting in a slower dissolution rate were selected. The purpose of this study was to study the role of sodium lauryl sulfate in the solid state on these interactions and their subsequent effect on drug dissolution.

Materials and Methods

Materials

The materials used in this study are listed in Table 1 which shows the two formulations in-

TABLE 1

Two formulations of ketorolac tromethamine

Formulation	Ingredients	Content (mg per capsule)
I	Ketorolac tromethamine	10.00
	Crospovidone, NF	9.00
	Lactose, spray dried, USP	428.30
	Magnesium stearate, NF	2.25
	Sodium lauryl sulfate, USP	0.45
II	Ketorolac tromethamine	10.00
	Crospovidone, NF	9.00
	Lactose, spray dried, USP	428.75
	Magnesium stearate, NF	2.25

vestigated. The concentration of drug, crospovidone (GAF Corp., New York, NY), magnesium stearate, NF (Mallinckrodt, St. Louis, MO) and the total weight per capsule remained constant in both formulations. The drug, ketorolac tromethamine (tromethamine salt of (±)-5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2-α]pyrrolo-1-carboxylic acid), had a purity of at least 99% and was obtained from the Institute of Organic Chemistry (Syntex Research, Palo Alto, CA). Formulation I contained additional 0.1% sodium lauryl sulfate (DuPont Chemical & Pigment, Wilmington, DE) as lubricant. Both formulations contained lactose, USP (Foremost, San Francisco, CA) as a filler.

Capsule preparation

The materials were mixed in a small planetary mixer (Kitchen Aid, Model K5-A; Hobart Manufacturing, Troy, OH) and comprised 50% of the mixer capacity. The rotation speed of the mixer was kept constant at 35 rpm. Preblends of drug, disintegrant and diluent without the lubricant were mixed for 25 min. Magnesium stearate, with or without sodium lauryl sulfate, was then added and mixed for 2, 5, 10, 20 and 28 min. Ten spot samples for each of these mixing times were withdrawn from different locations in the powder mixture and assayed for drug homogeneity. Samples were then filled by hand into hard gelatin capsules of size zero. Each capsule was individually weighed before and after filling.

Experimental methods

Drug homogeneity for 450-mg samples (447.3 and 447.75 mg for formulation I and II, respectively, both before mixing with lubricant) was determined by dissolving and extracting the samples in purified water. The undissolved excipients were removed by filtering the sample through a membrane filter (Millipore, Bedford, MA) with a pore diameter of 2 μm. The first 10 ml of the filtered solution was discarded to account for any possible absorption of the solute by the membrane filter. An aliquot of the filtrate was then diluted with purified water and its ultraviolet absorbance was measured at 322 nm on an ultraviolet spectrophotometer (Unicam SP 1800, Pye Unicam, Cambridge, U.K.).

The USP method for hard gelatin capsules was used to measure disintegration time for each capsule. The mean and standard deviation were calculated for the disintegration times of six capsules from each powder sample.

USP Method II was used to determine in vitro dissolution. Six capsules were tested for each determination. The testing apparatus consisted of USP paddles driven by a multiple-spindle drive with a variable-speed control (Model 72R, Hanson Research, Northridge, CA), 1-liter round-bottom plastic resin kettles (Elanco, Indianapolis, IN) and a water bath. The dissolution medium consisted of 500 ml of deaerated water equilibrated at 37°C and stirred at 50 rpm; whereas in the case of the control experiment, the dissolution medium consisted of sodium lauryl sulfate dissolved in the deaerated water, at a concentration of either 0.45 or 500 mg per 500 ml, equilibrated at 37°C and stirred at 50 rpm. The dissolved drug was analyzed by recording its ultraviolet absorbance at 322 nm, using an automated monitoring system consisting of a peristaltic pump (Model 1210, Harvard Apparatus, Millis, MA), 1 mm spectrophotometer flow cell, and an automatic sample changer/spectrophotometer (Model 25, Beckman, Fullerton, CA). The absorbances were plotted on a recorder every minute until complete dissolution was achieved. Calibration of the apparatus using USP dissolution calibrator tablets (prednisone, 50 mg) indicated that the mean dissolution and standard deviations were within the required range.

Powder samples withdrawn from the mixtures after different mixing times were evaluated using a scanning electron microscope (Model Alpha-9, International Scientific Instruments, Santa Clara, CA). To carry out this procedure, a small amount of powder was transferred to a piece of double-stick tape, which was then mounted on a cylindrical specimen stub. Surface conductivity on the powder sample was created by coating the sample with a silver paste in a vacuum evaporator (Polaron Instruments, Doylestown, PA). The samples were viewed in a scanning electron microscope at an oblique angle of 45°. Photographs were taken using a self-developing film (type 52 Polapan, Polaroid, Cambridge, MA).

Results and Discussion

Drug homogeneity

The drug contents from the samples of the two formulations throughout the mixing study ranged from 94 to 99%, the standard deviations being within 1.2–3.3%.

Disintegration time

The effect of mixing time (after the addition of lubricant) on the disintegration time of the hand-filled, uncompacted capsules is shown in Fig. 1. The disintegration time of capsules containing 0.5% magnesium stearate and 0.1% sodium lauryl sulfate remained relatively constant throughout mixing. Capsules containing 0.5% magnesium stearate, however, exhibited a small, gradual increase in disintegration time with prolonged mixing time.

Drug dissolution rate

The dissolution profiles of uncompacted capsules containing formulation I showing the effect of mixing time on in vitro dissolution before and after the addition of magnesium stearate and sodium lauryl sulfate are shown in Fig. 2. The results indicated that prolonged mixing with 0.5% magnesium stearate and 0.1% sodium lauryl sulfate did not adversely affect the dissolution rate of the drug in this formulation. An excellent correlation between disintegration time and dissolution rate is also evident from these results. Fig. 3 shows the drug dissolution profiles for capsules containing magnesium stearate as a lubricant. The data show a definite deleterious effect on the drug dissolution rate after prolonged powder mixing with magnesium stearate. Following 28 min of mixing, only about 20% of the drug dissolved after 30 min. Fig. 4 compares the dissolution profiles for capsules of both formulations I and II, each having been mixed with the lubricant(s) for 2 and 28 min. As can be seen from Fig. 4, the addition of 0.1% sodium lauryl sulfate in the solid state, introduced simultaneously with the 0.5% magnesium stearate,

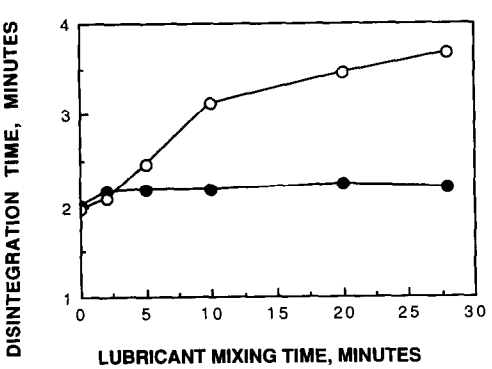


Fig. 1. Effect of mixing time on the disintegration time of capsules after the addition of lubricant(s). (●) 0.5% magnesium stearate +0.1% sodium lauryl sulfate (formulation I); (○) magnesium stearate (formulation II).

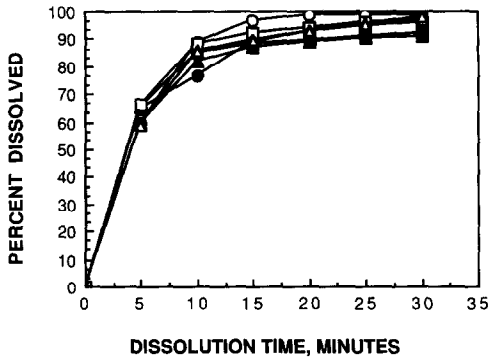


Fig. 2. Dissolution profiles for capsules containing formulation I, showing the effect of mixing time on in vitro dissolution before and after the addition of lubricants (0.5% magnesium stearate and 0.1% sodium lauryl sulfate). (●) 25 min mixing without lubricants; lubricants added and mixed for (○) 2, (■) 5, (□) 10, (▲) 20 and (△) 28 min.

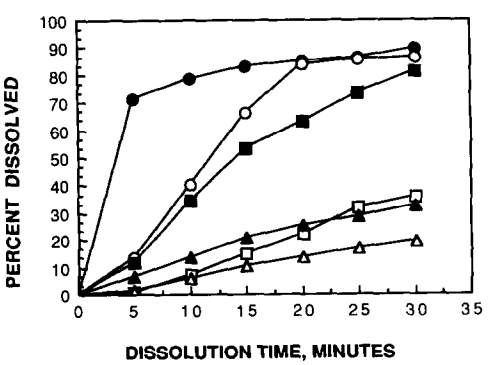


Fig. 3. Dissolution profiles for capsules containing formulation II, showing the effect of mixing time on in vitro dissolution before and after the addition of magnesium stearate. (●) 25 min mixing without magnesium stearate; magnesium stearate added and mixed for (○) 2, (■)5, (□) 10, (▲) 20 and (△) 28 min.

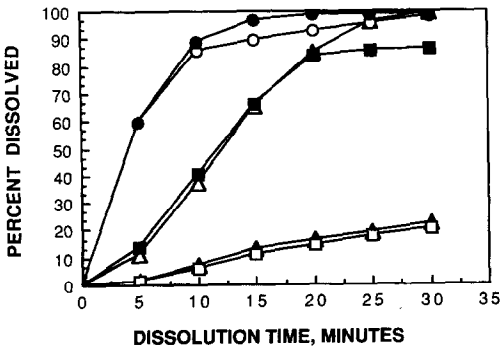


Fig. 4. Dissolution profiles for hand-filled, uncompacted, capsules containing formulations I and II, mixed for different periods of time after the addition of lubricant(s). (●) Formulation I, mixed with both lubricants for 2 min (dissolution medium – deaerated water); (○) formulation I, mixed with both lubricants for 28 min (dissolution medium – dearated water); (■) formulation II, mixed with magnesium stearate only for 2 min (dissolution medium – deaerated water); (□) formulation II, mixed with magnesium stearate only for 28 min (dissolution medium – deaerated water); (▲) formulation II, mixed with magnesium stearate only for 28 min (dissolution medium – water containing 0.45 mg sodium lauryl sulfate); (△) formulation II, mixed with magnesium stearate only for 28 min (dissolution medium – water containing 500 mg sodium lauryl sulfate).

does not adversely affect the drug dissolution rate. This phenomenon is more pronounced after prolonged powder mixing for 28 min. Formulation I exhibits a similar dissolution profile independent of the lubricant blending time, whereas formulation II shows markedly decreased dissolution rate with prolonged mixing with magnesium stearate. The markedly decreased dissolution rate of formulation II with prolonged magnesium stearate mixing time has been clearly elucidated in previous studies (Chowhan and Chi, 1985a,b, 1986a,b). Prolonged mixing with magnesium stearate decreased the rate of drug dissolution due to interactions between magnesium stearate, drug and excipients. The similar drug dissolution profiles of formulation I with prolonged lubricant mixing time could be due to either the reduced drug-excipient interaction with magnesium stearate or the better wetting of drug and/or magnesium stearate in the presence of sodium lauryl sulfate. To study this effect further, an equivalent amount of sodium lauryl sulfate added to the capsule was dissolved in the dissolution medium (0.45 mg/500 ml). In the second experiment, the amount of sodium lauryl sulfate in the dissolution medium was increased to more than 1000-fold (500 mg/500 ml). The dissolution test was performed using capsules of formulation II which was overmixed for 28 min with magnesium stearate. It is first assumed that strong particle-particle interactions exist between the magnesium stearate and the drug-excipient, and that none occur between the sodium lauryl sulfate and the rest of the drug and/or excipient during the prolonged powder mixing. Since sodium lauryl sulfate is an effective surfactant which may provide effective wetting of magnesium stearate on the surface of the drug-excipient agglomerates, one might assume that the improved dissolution profile of formulation I is due to the solution-mediated effect of sodium lauryl sulfate. If this is the case, then the dissolution of formulation II in a medium containing an equivalent concentration of sodium lauryl sulfate (0.45 mg/500 ml) should be better than that in its absence. As can be seen from Fig. 4, formulation II showed similar dissolution with or without an equivalent amount of sodium lauryl sulfate added to the dissolution medium. The result of this control experiment did not support this assumption. One may then argue that during the wetting of formulation I, the local concentration of sodium lauryl sulfate in the solid mixture at the time of contact with the dissolution fluid is greater than the so-called equivalent concentration because of the high aqueous solubility of sodium lauryl sulfate. The results for the dissolution of capsules of formulation II in a dissolution medium containing more than 1000-fold the amount of sodium lauryl sulfate compared to that used in the solid state showed a substantially improved dissolution rate. Nonetheless, the drug dissolution rate was still lower than that of formulation I. This result clearly indicated that the effect is not just due to the very effective wetting of magnesium stearate. It is also doubtful that dry mixture of formulation I eliminates much of the surfactant penetration time due to the location of the solid surfactant in the powder blend. This is because the dissolution profiles of formulation I remain almost unaffected by the prolonged powder mixing time. Another possible explanation would be to assume that there is less particle-particle

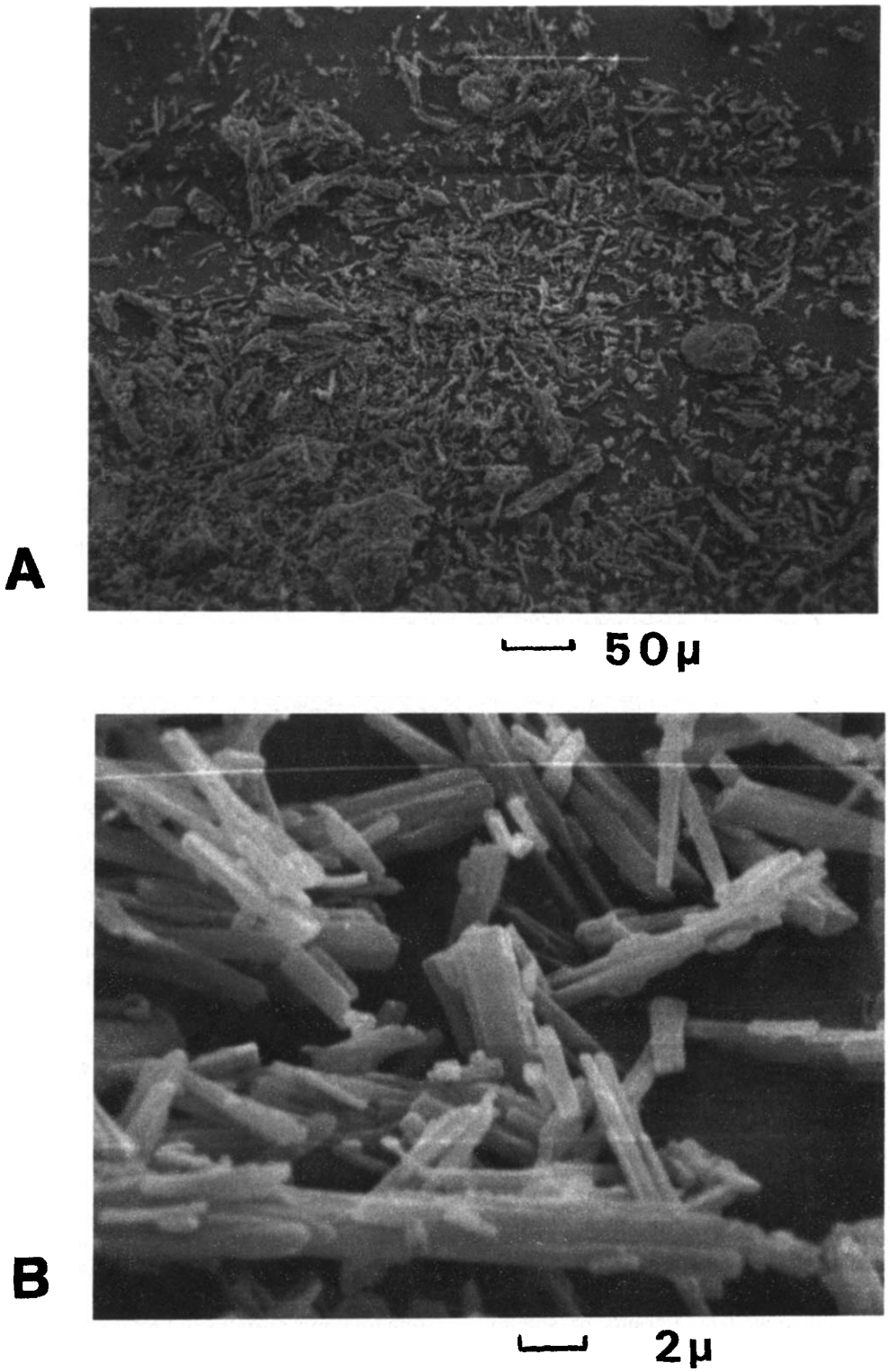
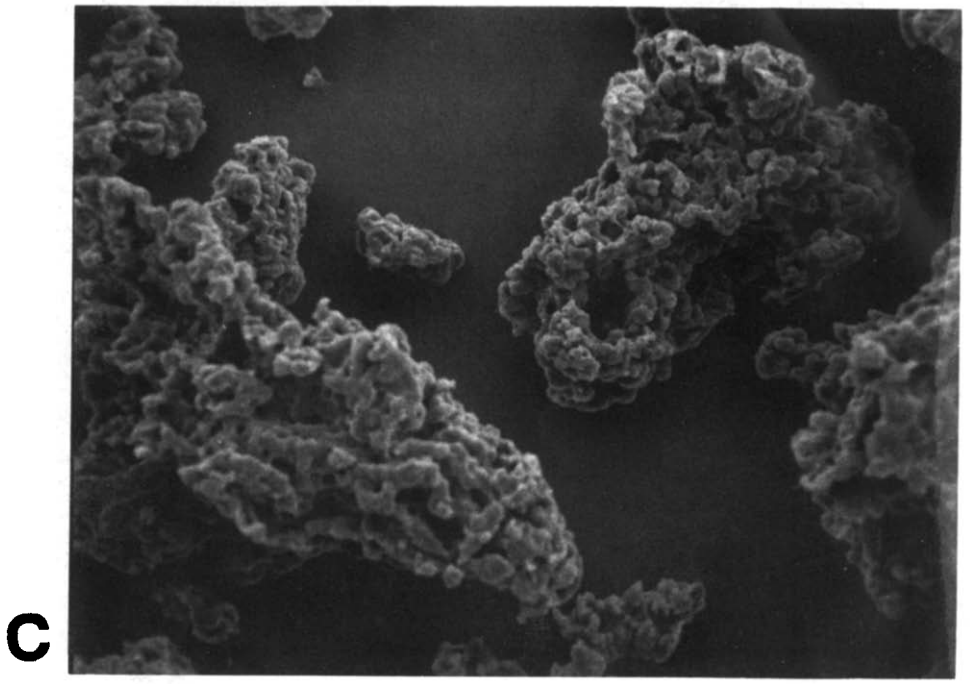
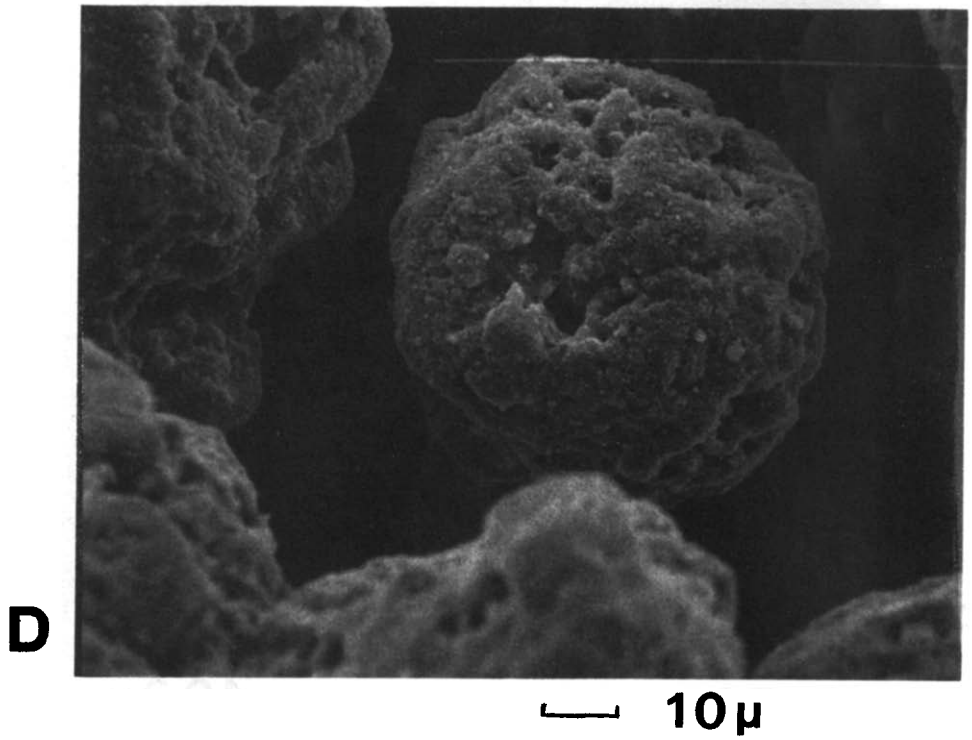


Fig. 5. Scanning electron micrographs of: (A) ketorolac tromethamine (×200), (B) ketorolac tromethamine (×5000), (C) crospovidone (×400), (D) spray-dried lactose (×1000), (E) magnesium stearate (×400), (F) sodium lauryl sulfate (×100).





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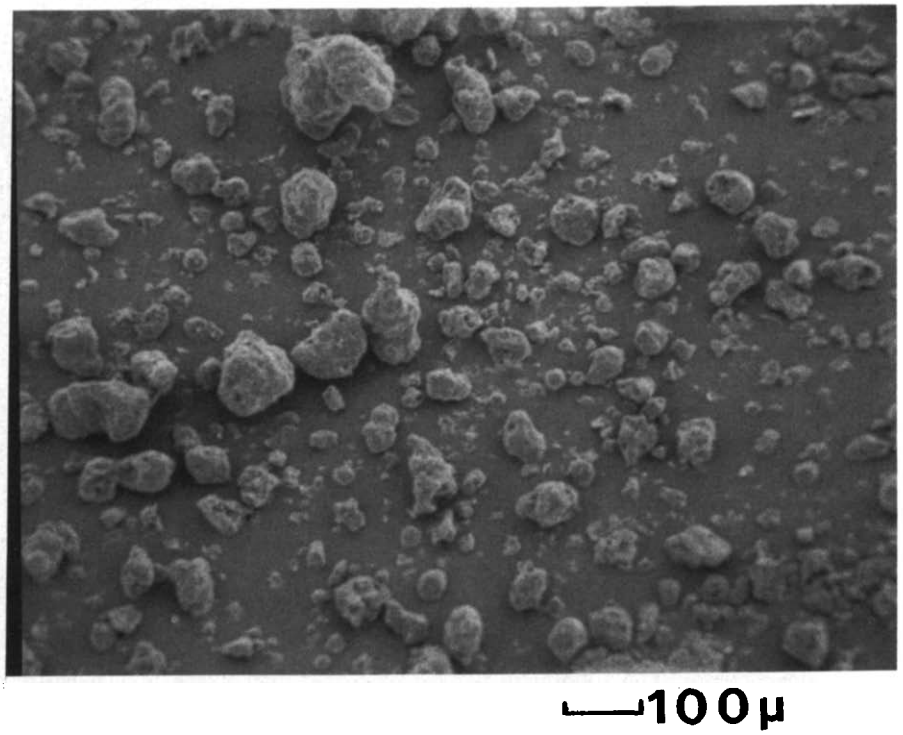

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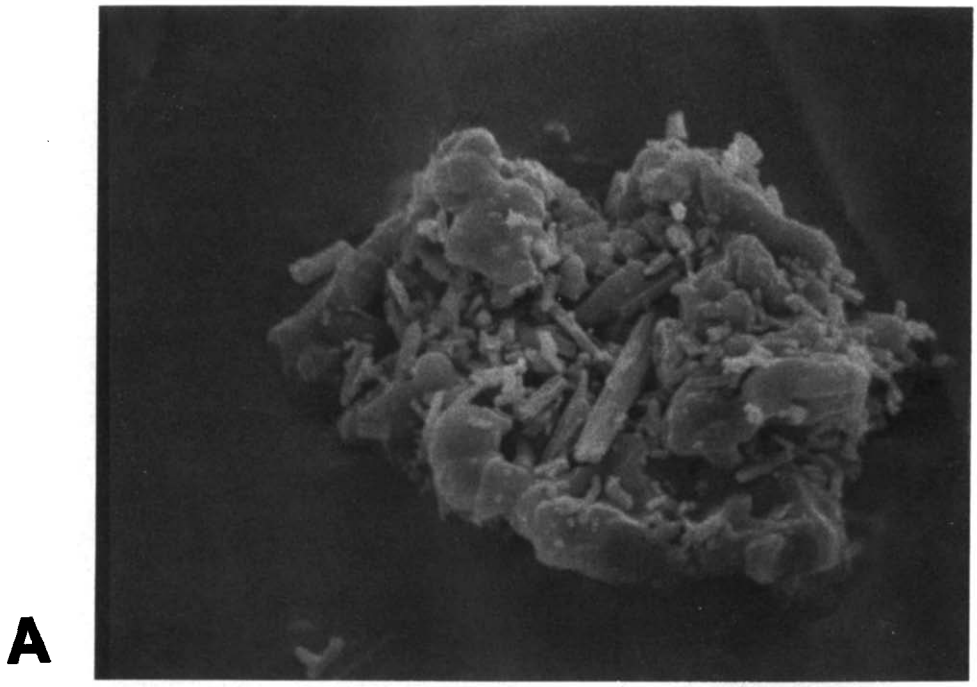


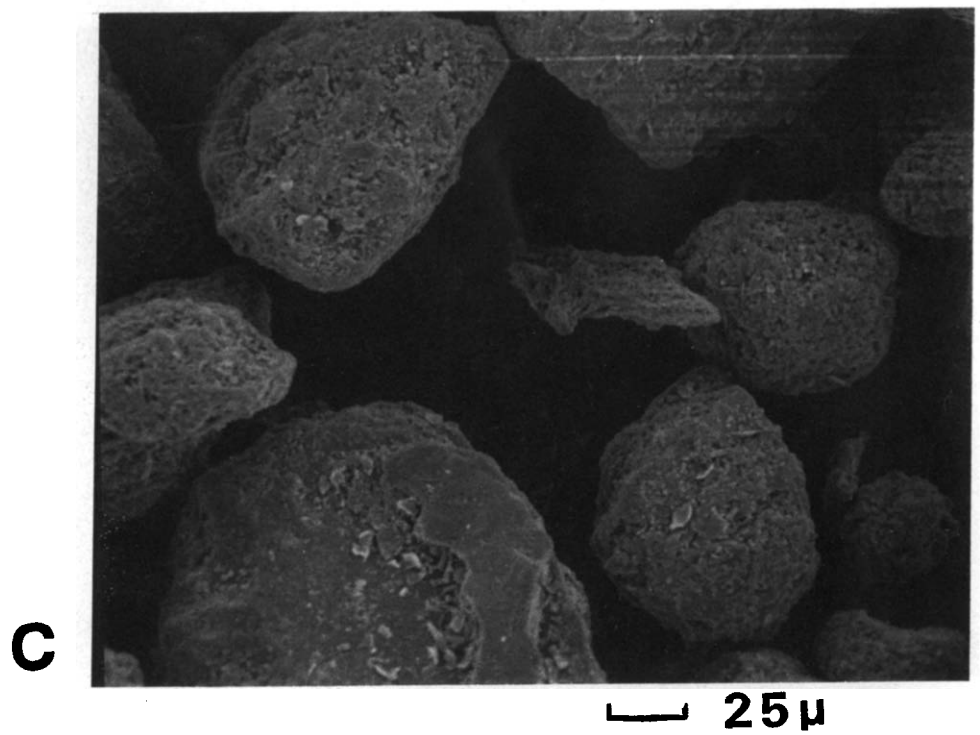
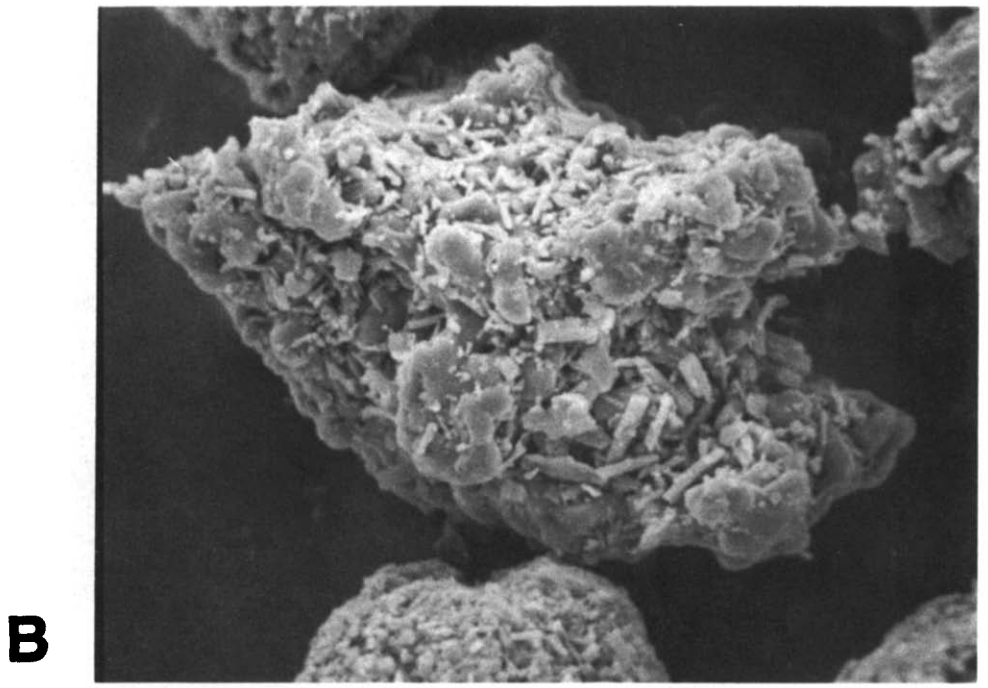
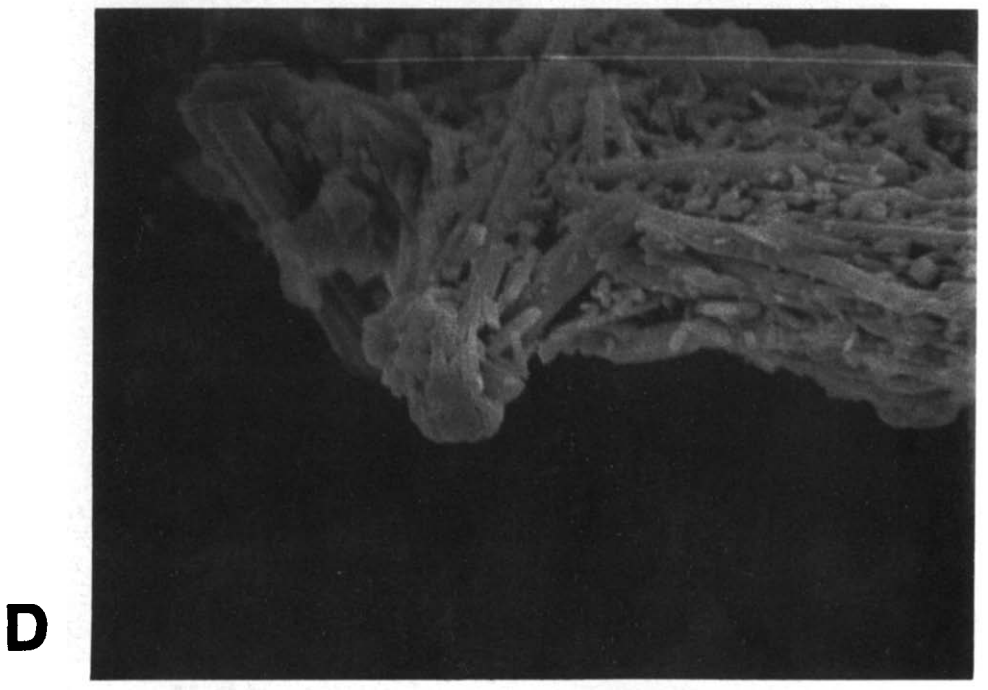


Fig. 6. Scanning electron micrographs of powder mixture with 0.5% magnesium stearate and 0.1% sodium lauryl sulfate (formulation I). (A) Without lubricants (×2000), (B) after 2 min of mixing with the lubricants (×1000), (C and D) after 10 min of mixing with the lubricants (×400 and ×2000, respectively), (E) after 20 min of mixing with the lubricants (×2000), (F–H) after 28 min of mixing with the lubricants (×1000, ×400 and ×1000, respectively).





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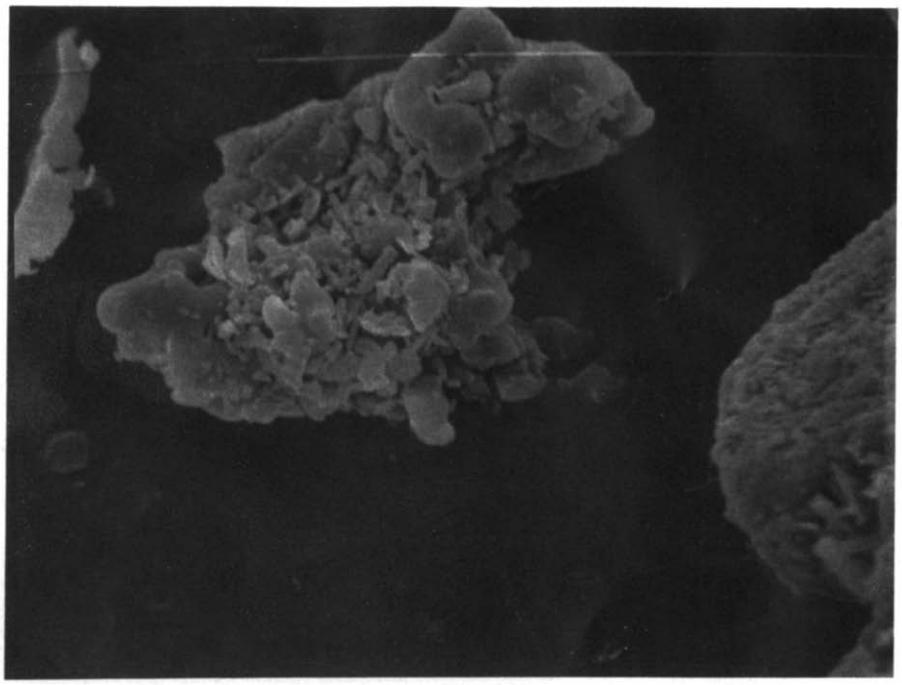

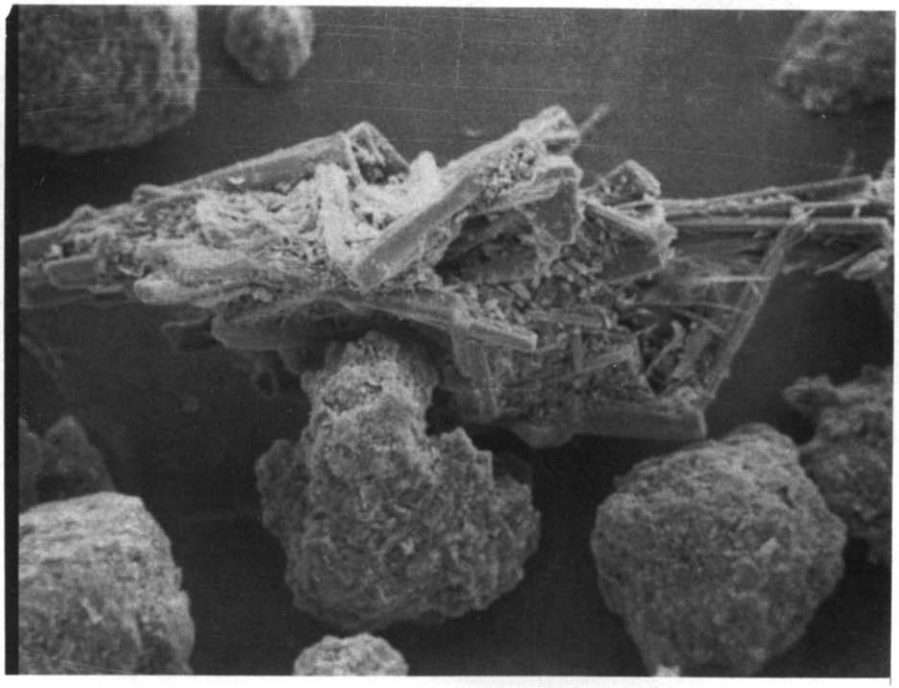

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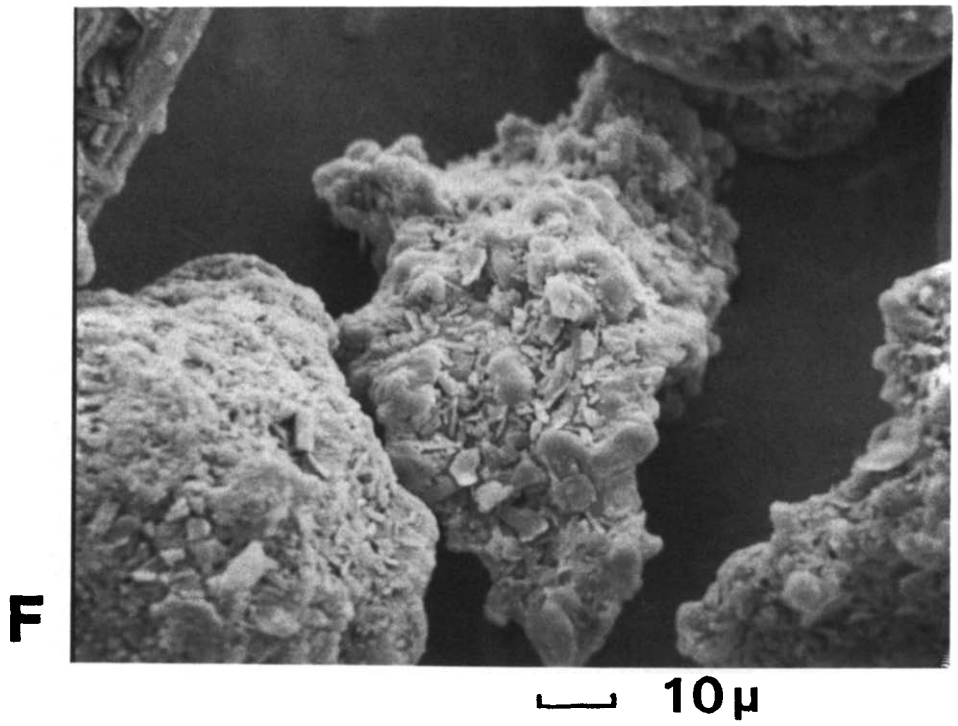


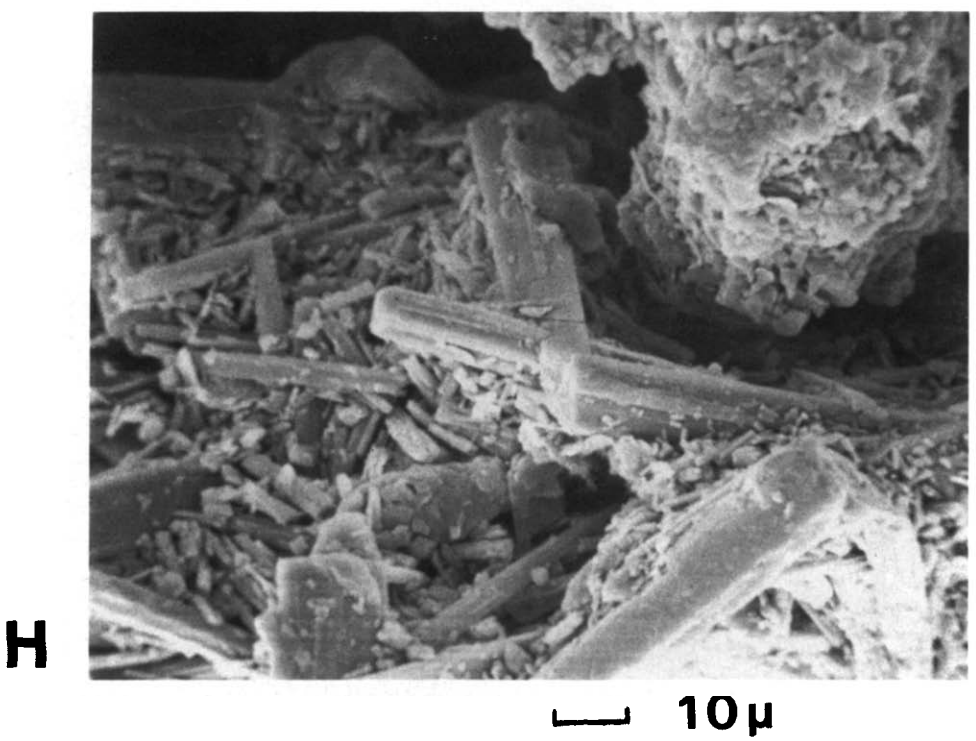


Fig. 6 (continued).

interaction between magnesium stearate and the drug-excipient agglomerates due to the presence of sodium lauryl sulfate. The question then arises as to the manner in which sodium lauryl sulfate exerts an effect during the solid-solid interaction. That is, does it facilitate the removal of magnesium stearate from the surface of drug-excipient agglomerates or does it simply have strong binding characteristics with drug-excipient agglomerates and thereby provide a better wetting of drug particles? In order to substantiate further the finding from the above dissolution data, a scanning electron microscope was used to examine the two formulations.

Scanning electron micrographs

The scanning electron micrographs (SEMs) of the starting materials are shown in Fig. 5. Mixing of the drug, ketorolac tromethamine, with lactose and crospovidone for 25 min, resulted in interaction between the smaller drug particles and crospovidone agglomerates being observed (Fig. 6A). One can see that smaller drug particles were entrapped in the large porous structure of crospovidone particles. After 25 min pre-mixing, 0.5% magnesium stearate and 0.1% sodium lauryl sulfate were added and powder samples were withdrawn at selected mixing time intervals. It appears that, during the additional blending with the lubricants, agglomeration of drug particles occurred (Fig. 6C and D). Some adhesion of the magnesium stearate toward the drug-crospovidone agglomerates can be seen (Fig. 6B, D and E); however, this interaction was slight. After 28 min of mixing with both magnesium stearate and sodium lauryl sulfate (Fig. 6F–H), it appears that the agglomeration of the drug particles prevails over the flaking of the magnesium stearate particles. The interaction between the drug agglomerates and magnesium stearate flakes is not visible. This lack of particle-particle interactions between drug and magnesium stearate and/or between the drug-crospovidone agglomerates resulted in identical dissolution profiles before and after prolonged mixing with the lubricants. It was not possible to locate the sodium lauryl sulfate particles in the powder blend, since the amount of sodium lauryl sulfate in the powder mixture is small ($\sim 0.1\%$). Powder mixtures containing sodium lauryl sulfate and magnesium stearate in a ratio of 1 : 5 were prepared in order to simulate their ratio in the powder blend for SEM examination. The powder mixture was mixed for 28 min and samples were withdrawn at specific mixing intervals for SEM observation. The SEMs (Fig. 7) reveal that strong particle-particle interactions take place between the magnesium stearate flakes and the sodium lauryl sulfate particles. Sodium lauryl sulfate remained intact whereas magnesium stearate delaminated, 'spreading' over the surface of sodium lauryl sulfate. Fig. 7A shows the surface morphology of a sodium lauryl sulfate particle before blending with magnesium stearate. The surface was covered with magnesium stearate flakes after prolonged mixing with the magnesium stearate for 2 min (Fig. 7B), 10 min (Fig. 7C) and 28 min (Fig. 7D). This phenomenon resembles the spreading over the surface, i.e. surface adsorption, that was described in the paper of Shah and Mlodozeniec (1977). It is clear from these observations and the results from dissolution data that the mechanism of action of sodium lauryl sulfate in a powder mixing process possibly is through a strong physical interaction with the magnesium stearate. This strong interaction between the two lubricants may compete with the remaining agglomerates of drug or drug-crospovidone for affinity with magnesium stearate flakes. Subsequently, the bonding of particle-particle interactions between magnesium stearate and other drug-excipient particles may be inhibited. It is believed that this interaction may permit the removal of a previously formed magnesium stearate film from the surface of drug-agglomerates. It is possible that the combination of this particle-particle interaction and the surface-tension lowering capability (Levy and Gumtow, 1963) of sodium lauryl sulfate after wetting suppresses the deleterious effect of magnesium stearate on the in vitro drug release. Again, assuming that the wetting of sodium lauryl sulfate on the surface of the dry mixture of magnesium stearate and sodium lauryl sulfate is the dominant mechanism over the particle-particle interaction between magnesium stearate and sodium lauryl sulfate in counteracting the deleterious effect caused by prolonged mixing with magnesium stearate, the wetting of sodium lauryl sulfate must

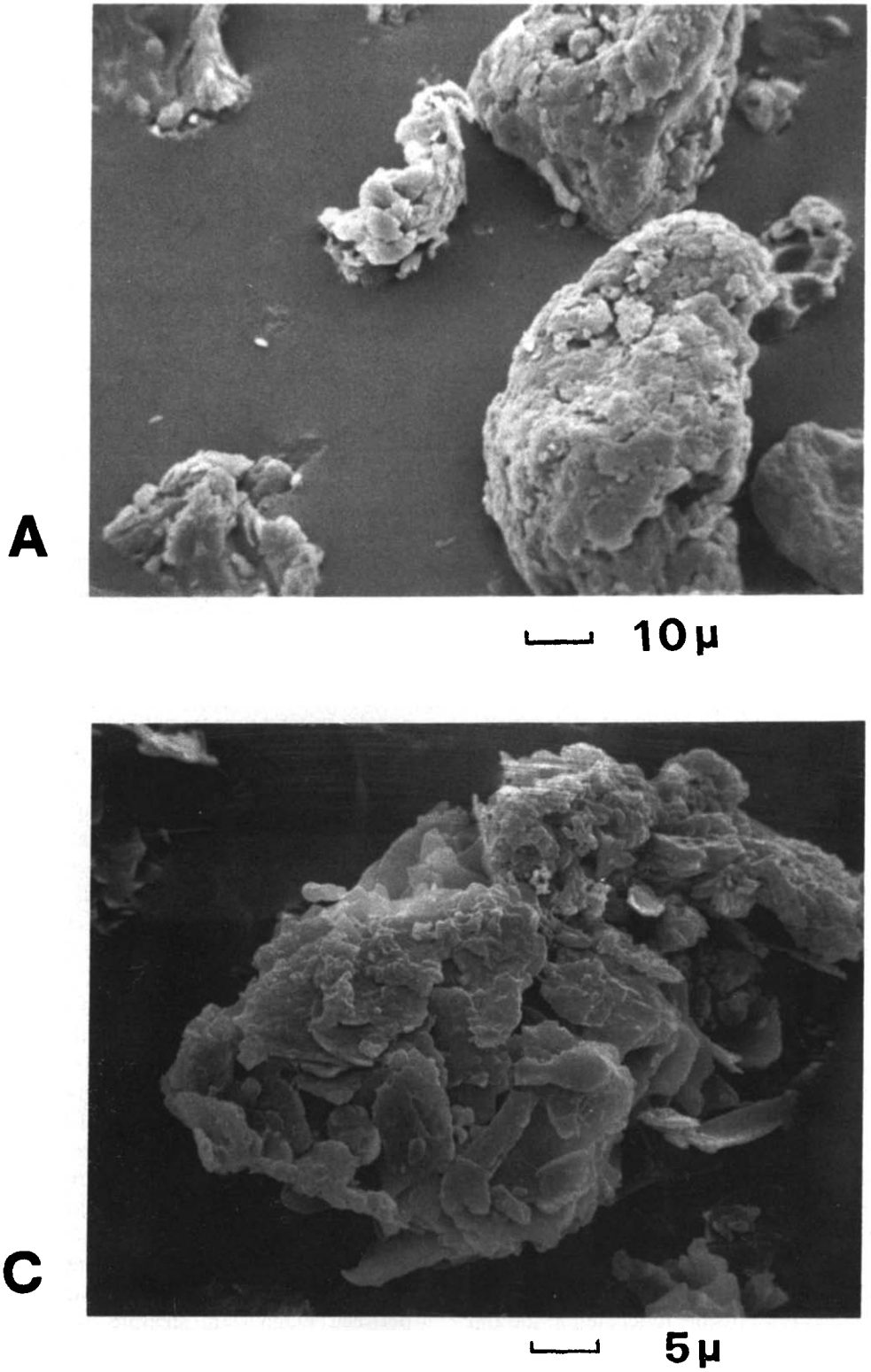
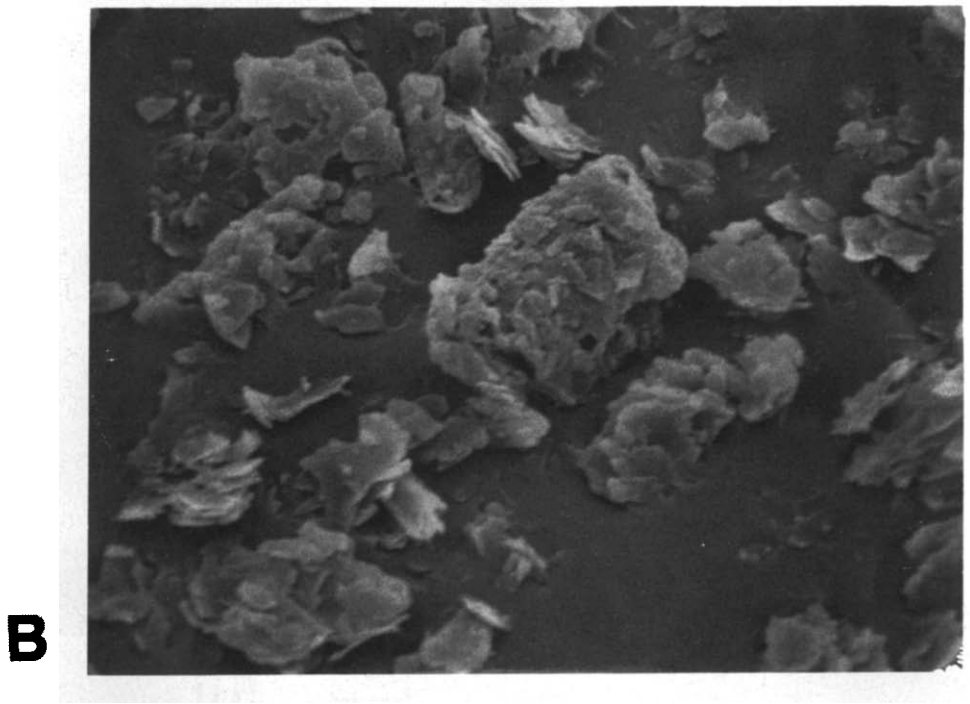
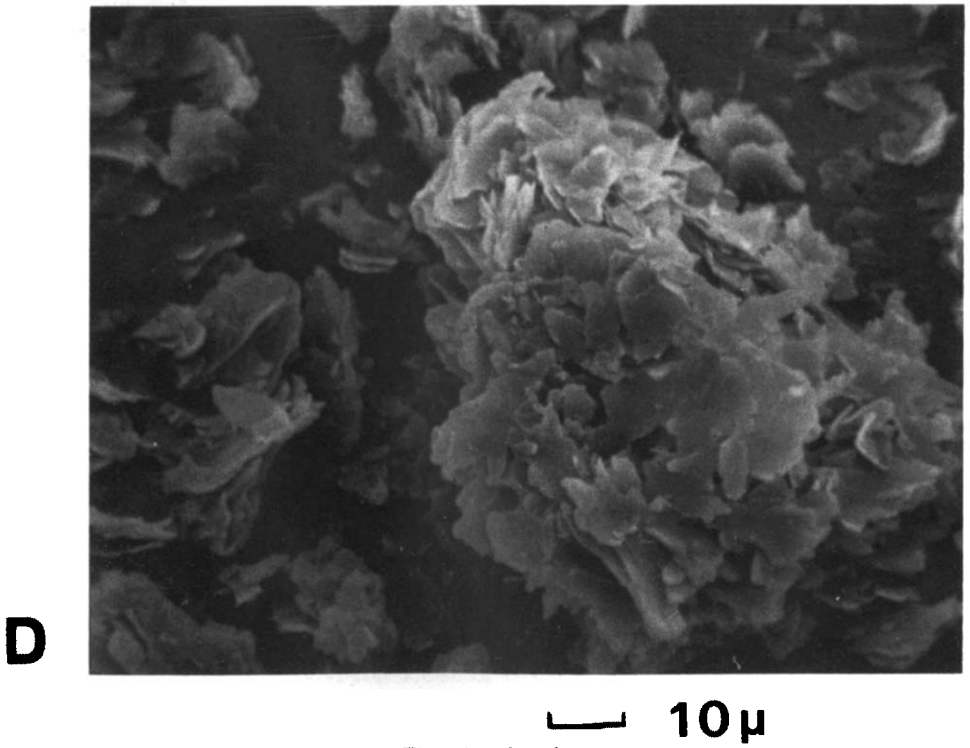


Fig. 7. Scanning electron micrographs of powder mixture of sodium lauryl sulfate and magnesium stearate in a ratio of 1 : 5. (A) Sodium lauryl sulfate particles before mixing with magnesium stearate (×1000), (B) after mixing with magnesium stearate for 2 min (×1000), (C) after mixing with magnesium stearate for 10 min (×2000), (D) after mixing with magnesium stearate for 28 min (×1000).





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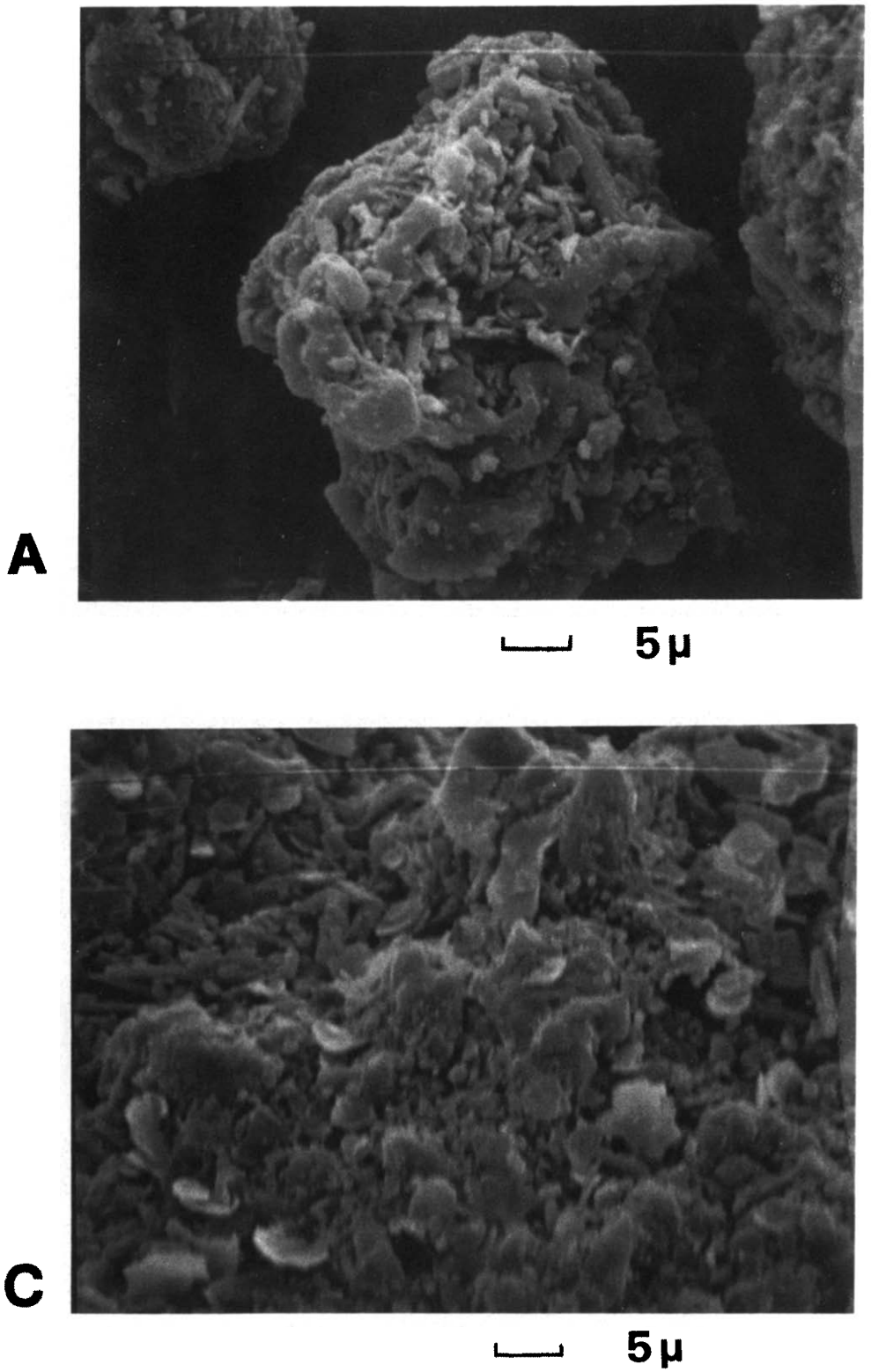
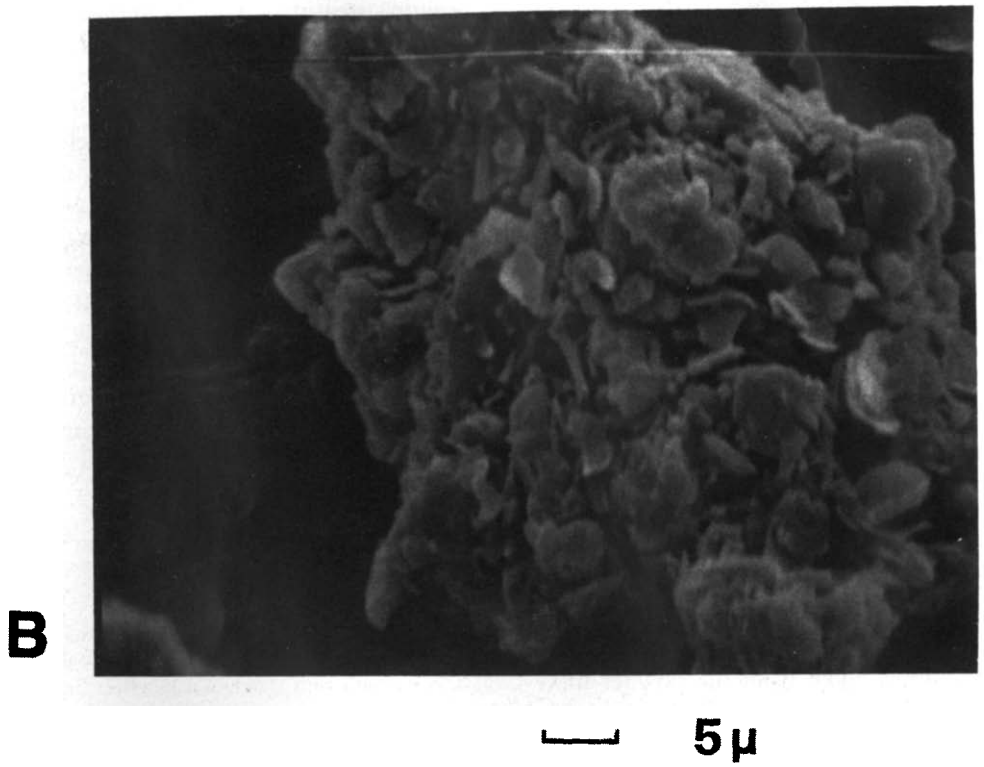


Fig. 8. Scanning electron micrographs of powder mixture with 0.5% magnesium stearate (formulation II). (A) Without lubricant (×2000), (B) after 5 min of mixing with the lubricant (×2000), (C) after 20 min of mixing with the lubricant (×2000), (D) after 28 min of mixing with the lubricant (×2000).



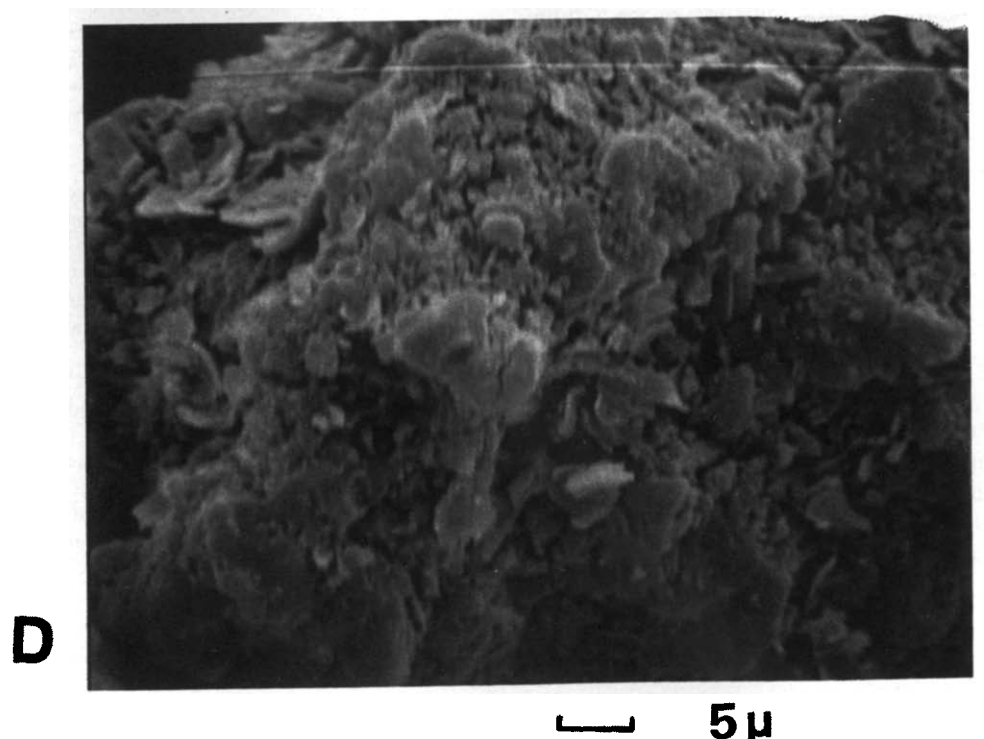


Fig. 8 (continued).

first overcome the hydrophobic barrier of magnesium stearate which is now coated on the surface of sodium lauryl sulfate. The wetting of the dry mixture hence becomes a progressive process and the local concentration cannot be greater than the 1000-fold used in the control experiment. This would mean that the drug dissolution rate might be hindered due to the ineffective wetting of magnesium stearate, and the impeded surfactant penetration time due to the location of the solid surfactant in the powder bed. Nonetheless, the drug dissolution data showed just the opposite. Clearly, the effect cannot be entirely due to the very effective wetting of the magnesium stearate. This supports the postulate that wetting of magnesium stearate is secondary to the particle-particle interaction between magnesium stearate and sodium lauryl sulfate. Fig. 8 demonstrates the drug-excipient interaction of the powder mixtures of formulation II after prolonged mixing with magnesium stearate. Fig. 8A shows SEMs of formulation II samples taken from the powder mixtures before blending with magnesium stearate. It shows that smaller drug particles were entrapped in the large porous structures of crospovidone particles. Fig. 8 (B–D) illustrates that prolonged mixing of magnesium stearate with the powder mixture resulted in the flaking of magnesium stearate and subsequent adhesion of the magnesium stearate flakes toward the drug-crospovidone agglomerates. The results of these interactions was a significant reduction in the drug dissolution rates.

Conclusion

The results of this study demonstrate that sodium lauryl sulfate, when added simultaneously to magnesium stearate in the solid state in 1 : 5 ratio, can suppress the retardation of in vitro dissolution caused by prolonged mixing of magnesium stearate. The examination of powder blends at various mixing intervals under the scanning electron microscope suggests that the solid-state property of sodium lauryl sulfate is the major factor in counteracting the deleterious effect caused by magnesium stearate. Sodium lauryl sulfate interacts strongly with magnesium stearate flakes, reducing the surface coating of magnesium stearate on drug-excipient agglomerates, after prolonged mixing. Magnesium stearate appears to be detached from the surface of the drug-excipient agglomerates due to the stronger interaction with sodium lauryl sulfate thus minimizing the effect of prolonged mixing with the lubricant on drug dissolution.

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